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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,183	11/14/2001	Alan Gewirtz	43826-9	6995

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George A. Frank
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996

EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,183	GEWIRTZ, ALAN	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-9,11,14 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-9,11,14 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 02/01/2005 and 03/04/2005 have been entered.

Status of Application/Amendment/Claims

2. Claims 1, 2, 5, 7-9, 11, 14, and 17-22 are pending in this application.

Applicant's response filed 02/01/05 and 03/04/2005 with the instant request for continued examination has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 10/06/2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 5, 7-9, 11, 14 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office Action mailed 10/06/2004 (sections 2 and 3, pgs. 2-5).

Response to Arguments

5. Applicant's arguments filed 02/01/2005 and 03/04/2005 have been fully considered but they are not persuasive. In regards to the outstanding rejection under 35 U.S.C. § 112 1st paragraph, written description, Applicant has argued that the written description requirement is viewed in light of the state of the art and the skill of the practitioner at the time the application was filed (pg. 3, 2nd paragraph) and that it is clear that the invention need not be described *ipsis verbis* for the purposes of written description but rather that what is needed is that the skilled artisan understand, based on the disclosure of the specification as filed and the knowledge imputed to the skilled artisan at the time the specification was filed, that the inventor has possession of the claimed subject matter and that one skilled in the art, upon reading the specification, would have understood what was meant by an RNA that is homologous to any target

gene and that thus, Applicant was in posession of the claimed invention (pg. 6, 4th and 5th paragraphs). This argument is not found persuasive for the reasons of record set forth in the Office Action mailed 10/06/05, which considers that the disclosure of the specification and the teachings of the prior art, as a whole, fail to provide or point to the structure of an RNA that can have any degree of homology to any target gene, that is commensurate with what is claimed, that will provide the function of RNA interference to any cell.

Applicant also argues that the degree of homology for the claimed invention is inherently disclosed in the examples of the specification and would have been recognized by one of skill in the art because the specification teaches the *in vitro* transcription of RNA from a DNA template that provides the sequence to which a homologous RNA is desired and the annealing of this RNA to form dsRNA (pg. 6, last paragraph bridge to pg. 7). Applicant then presents arguments concerning the error rates of RNA polymerases. However, it is not clear how this latter argument addresses the outstanding grounds of rejection. Applicants arguments do not provide or point to the structure of an RNA wherein that RNA can have any degree of homology to any target gene, that is commensurate with what is claimed, that will provide the function of RNA interference to any cell.

Applicant also argues that the specification provides teachings on the length of the dsRNA homologous to a target gene because the specification provides an example of a dsRNA molecule that is 828 bp long, therefore providing an upper limit on what sized dsRNA is successfully used in the method as claimed (pg. 7, last paragraph) and

that the lower limit on the size of the dsRNA is evident in the logic used in designing antisense molecules and that one skilled in the art recognizes that the minimum dsRNA size to achieve target specificity is 17 nucleotides. (bottom of pg. 7 bridge to pg. 8). This argument is not persuasive because examples drawn from Applicant's specification are exemplifications of the claimed invention and the instant claims are not limited to the subject matter as exemplified by Applicant. In regards to the minimum size of a dsRNA molecule, Applicant's arguments do not address the outstanding grounds of rejection in that they do not provide or point to a particular structure of an RNA that functions to initiate RNA interference that is comensurate with what is now claimed.

In summary, Applicant has argued that the specification teaches the degree of homology for the dsRNA used in the claimed invention as well as the size ranges for the dsRNA and the method of making dsRNA homologous to the target gene and that based on the disclosure and the knowledge of the skilled artisan at the time, a skilled artisan would understand that applicant had possession of the claimed subject matter (pg. 9, 1st paragraph). However, this argument is not found persuasive. Applicant has pointed to the Regents of the University of California v. Eli Lilly wherein the Court of Appeals for the Federal Circuit stated: "in claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." However, an analysis of the facts in the instant Application indicates that although the state of the art recognizes a general

formula for RNA, in that it is comprised of 4 types of nucleobases, the state of the art recognizes that what distinguishes one RNA from another RNA is the fact of primary nucleotide sequence. Without such primary nucleotide sequence information, there is no way for one skilled in the art to distinguish one RNA from another RNA such that one skilled in the art can identify many of the species that the claims encompass.

6. Claims 1, 5, 7, 9, 11, 14 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the Office Action mailed 10/06/2004; e.g., because these broad claims read on *in vivo* methods. It is noted herein that the instant specification, while not being enabling for methods of using RNAi to disrupt gene expression *in vivo*, is enabling for the specifically disclosed embodiment of using RNAi *in vitro*, to practice methods of disrupting KitR gene expression in human cancer cell lines using the disclosed KdsRNA.

Response to Arguments

7. Applicant's arguments filed 02/01/2005 and 03/04/2005 have been fully considered but they are not persuasive. Applicant has presented arguments that were previously presented in the communication filed 7/15/2004, that the present specification, including the working examples, contains ample direction on how to practice the full breadth of the claimed RNAi therapeutic method (pg. 10, 2nd and 3rd paragraphs). These arguments are not found persuasive for the reasons of record set forth in the Office Action mailed 10/06/2004 (see sections 4-5, pgs. 6-15). Applicant has

also argued that two of the references cited by the Examiner discuss the various successful ways nucleic acid is delivered *in vivo* to cells. Although Applicant is correct in pointing out that the abovementioned references do discuss the various successful ways nucleic acid can be delivered *in vivo*, to cells, neither of these references, taken as a whole, and as set forth in the prior Office Action, considers that the uptake and biological activity observed *in vitro,* will predictably translate to *in vivo* results, in part, at least, because formulations and techniques for delivery *in vitro* are often not applicable *in vivo*. Applicant further argues that recent work has shown that dsRNA can be successfully delivered *in vivo* using intravenous delivery methods as taught in the specification because the specification generally contempletes intravenous administration. However, Applicant's contention that these references make it clear that undue *de novo* trial and error expermentation is not necessary to carry out Applicant's invention is not persuasive because the determination of an enabling disclosure is made at the time of filing. These references were published several years after the filing of the instant application and therefore indicate that, at the time the instant invention was made, the state of the art nucleic acid therapeutics still required several years for the enablement of even a small number of nucleic acid therapeutics *in vivo*. In this regard, the skilled artisan, in order to practice the instantly claimed methods in their full scope, without carrying out undue, *de novo*, trial and error experimentation, would have required specific and substantial guidance not present in the specification as filed and not provided by the state of the art at the time of filing.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 2, 5, 7-9, 11, 21 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (U.S. Patent 6,506, 559) for the reasons of record as set forth in the Office Action mailed 10/06/2005 and reiterated herein. Fire et al. disclose a method for inhibiting expression of a target gene using double stranded RNA to induce RNAi in a cell *in vitro* (Column 26, claim 1) wherein the cell is from an animal (Column 26, claim 6). Fire et al. disclose that the cell with the target gene may be derived from or contained in any organism (column 8, line 13-14) and that examples of vertebrate animals include mammals and human (column 8, lines 35-37) and that the cell having the target gene may be "immortalized or transformed, or the like" (column 8, lines 52-55) and that "the present invention could be used for treatment or development of treatments for cancers of any type, including solid tumors and leukemias..." (Column 10, lines 26-28). Fire et al. disclose that lipid mediated carrier transport can be used to introduce nucleic acids to cells (Column 9, lines 55-60). Fire et al. also disclose that inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene (Column 6, lines 55-57), thereby indicating disruption of gene function (which is to produce protein).

Therefore, Fire et al. anticipate the instant invention as set forth in claims 1, 2, 5, 7-9, 11 and 22.

Response to Arguments

9. Applicant's arguments filed 02/01/2005 and 03/04/2005 have been fully considered but they are not persuasive. Applicant has argued that reduction to practice in the Fire et al. specification is limited to the invertebrate animal, *C. elegans* and that the disclosure regarding dsRNA induced inhibition in higher order, vertebrate cells, was sheer speculation (pg. 13, 3rd full paragraph). Applicant also argues that Fire, in papers authored after the filing date of US 6,506,559, makes clear the speculative nature of RNAi in mammalian cells and provides quotations from a) Montgomery and Fire (1998) TIG 14:255-258 and b) Fire (1999) *Trends Genet.* 15:358-363, that purportedly indicate that Fire considered that "one skilled in the art did not expect dSRNA to induce RNA interference in human cells" (pg. 13, 3rd full paragraph) and that "at the time of filing of the '559 patent, one skilled in the art, the inventor himself, did not believe his claimed methods would work in mammalian cells" (pg. 14, 1st full paragraph).

However, contrary to Applicant's argument, and as pointed out by Applicant in the instant response, reduction to practice is not required for a specification to be enabling. Additionally, although the individual quotations provided by Applicant appear to lend a degree of support to the instant argument when viewed outside of the context of the references, these quotations, taken in context of the references as a whole, do not make clear the speculative nature of RNAi in mammalian cells, but rather provide a review of known information regarding potential difficulties in the application of dsRNA

in mammalian cells and provide a reasonable means of overcoming said difficulties; e.g.; by using a controlled level of dsRNA. The discussions refered to are not speculation but rather, reasoned hypotheses, based on available evidence, which indicates that one skilled in the art could reasonably have expected that dsRNA could induce RNAi in mammalian (human) cells, particularly since the difficulties to be encountered and a means of overcoming these difficulties were set forth.

Moreover, the Fire et al. reference is a patent. The rejection under Fire is a rejection under claims in an issued patent, the enablement of which is presumed valid.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-00811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba